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Communication

Compatibility of Different Formulations in TrichoConcept™ Vehicles for Hair Treatments

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Abstract: The wide variety of potential pathogeneses for alopecia and the wide variety of active pharmaceutical ingredients (APIs) to treat and manage those pathogeneses highlight the importance of the development of stable and effective topical treatments. Topical options for alopecia on the market remain limited and oral products may result in unwanted systemic adverse effects. This study is meant to fill the gap by determining compatibility in terms of beyond-use date (BUD) of APIs with theoretical or demonstrated benefits for topical use for alopecia. The compatibility of seven formulations was tested: F1 = clobetasol 0.05% in TrichoWash™; F2 = ketoconazole 2% in TrichoWash™; F3 = spironolactone 1% in TrichoWash™; F4 = latanoprost 0.1% in TrichoCream™; F5 = pyridoxine HCl 0.5%, vitamin A acetate 1%, and vitamin E succinate 12.1 IU in TrichoCond™; F6 = Caffeine 2%, menthol 1%, and pyridoxine HCl 0.5% in TrichoWash™; F7 = Latanoprost 0.1%, minoxidil 5%, and finasteride 0.25% in TrichoSol™. All formulations presented a BUD of 6 months, except for F4 and F7, which showed compatibility for 3 months. This validates the compatibility of the APIs with the Trichotech™ vehicles, and that they are highly convenient for compounding pharmacies.

Keywords: alopecia; hair treatments; compounding pharmacy; TrichoConcept

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1. Introduction

Alopecia is a pervasive issue around the world. One study of men between the ages of 18 to 49 years, found that 42% of men had moderate to extensive hair loss. Evidence suggests that androgenetic alopecia, the most common form of alopecia, affects over half of men over 50 years of age; and in women, the reported incidence of alopecia is 29 to 38% for patients over 70 years of age [1,2]. Though alopecia itself often does not cause significant adverse health effects, it can increase and worsen anxiety and depression and those with alopecia often have lower self-esteem and body image [3].

Given the high incidence and significant psychosocial impact of alopecia, options for the management and treatment of hair loss are essential. Commercially available topical options are limited, and oral options can be related to possible adverse effects. In this study, we explored the compatibility of several active pharmaceutical ingredients (APIs) in bases designed to be used for patients with alopecia, including TrichoWash™ (a ready-to-use vehicle for personalized non-irritant shampoos), TrichoCond™ (a ready-to-use vehicle for personalized conditioners and with moisturizing properties), TrichoCream™ (a ready-to-use vehicle for personalized creams for eyelashes, eyebrows, and beards), and TrichoSol™ (a ready-to-use vehicle for personalized hair solutions; consisting of a highly spreadable hydrophilic solution containing mineral salts of vegetable origin and is free from alcohol and propylene glycol), each of which contains TrichoTech™, a patented technology designed to promote scalp health. All vehicles are free from parabens, formaldehyde, PABA, boric acid, benzyl alcohol, benzyl benzoate, propylene glycol, lanolin, triclosan, 1,4-dioxane, petrolatum, and artificial colorants [4].

The chosen APIs were caffeine, clobetasol propionate, finasteride, ketoconazole, latanoprost, menthol, minoxidil, pyridoxine hydrochloride, spironolactone, vitamin A acetate, and vitamin E succinate. Those comprised FDA-approved APIs for androgenetic alopecia (finasteride, minoxidil, and dutasteride) and also APIs with scientific evidence of potential for such conditions, either in isolation or as add-on therapies. Studies evaluating caffeine have found that topical preparations can significantly increase the number of hairs in anagen phase (growth phase) [5]. Its safety and efficacy profile based on current information warrants studies to ensure compatibility in topical vehicles. Clobetasol propionate is a steroid that has demonstrated efficacy in adults as well as pediatric patients suffering from alopecia areata [6,7]. Alternatively, finasteride for topical use has been well studied at a variety of strengths for androgenetic alopecia; the topical use allows the successful treatment of alopecia while avoiding higher systemic levels associated with oral use [8–10]. Similar to finasteride, spironolactone is another anti-androgenic drug that has been studied for topical use to avoid unwanted adverse effects that may be associated with oral use, such as those associated with its mechanism of action as a diuretic [11]. Other options such as latanoprost or minoxidil have a history of topical use but may not be available at the appropriate strength for use on the scalp, such as in the case of latanoprost or, as is the case with minoxidil, are often available in hydroalcoholic vehicles or vehicles that contain propylene glycol, which may cause drying or irritation of the scalp or even contact dermatitis [12,13]. In addition to these APIs, other vitamin deficiencies have been linked to hair loss as well, and topical options for these vitamins, such as pyridoxine, vitamin A, or vitamin E may help to support a healthy scalp and correct deficiencies that may be contributing to hair loss or lack of new hair growth [14].

The wide variety of potential pathogeneses for alopecia and the wide variety of APIs to treat and manage those pathogeneses highlight the importance of the development of stable and effective topical treatments. Topical options for alopecia on the market remain limited and oral products may result in unwanted systemic adverse effects. This study is meant to fill the gap by determining the compatibility of active ingredients with theoretical or demonstrated benefits as a topical option for alopecia. In this study ketoconazole, clobetasol propionate, spironolactone, and latanoprost were evaluated as individual agents in vehicles designed for topical use on the scalp for alopecia. Combination products of pyridoxine HCl, vitamin E, and vitamin A, as well as caffeine, menthol, and pyridoxine, and lastly, a combination of latanoprost, minoxidil, and finasteride were evaluated as combination formulations to demonstrate compatibility in bases well-suited for use for alopecia.

2. Materials and Methods

2.1. Preparation of Active Pharmaceutical Ingredients Cream Samples

The composition of the seven tested samples is described in Table 1. Those formulations (qualitative composition and concentrations) were chosen within the context of personalized medicine, meaning that compounding pharmacies often receive those prescriptions with doses and combinations different from the products available in the market, so to offer unique treatments for some patients. All formulations were prepared as described below and all materials were provided by Fagron (Saint Paul, MN, USA).

F1. Clobetasol 0.05% in TrichoWash™

1. Weigh clobetasol propionate in a hood;
2. Measure approximately 50% of the required TrichoWash™ and incorporate clobetasol propionate until a paste is obtained, using glass mortar and pestle;
3. Transfer to a light-resistant polyethylene dispensing container, adding the required total amount of TrichoWash™, rinsing the mortar;
4. Adjust pH to 4.0–5.0 with triethanolamine, if needed.

F2. Ketoconazole 2% in TrichoWash™

1. Weigh ketoconazole in a hood;
2. Dissolve ketoconazole with DMSO, using glass mortar and pestle;

3. Slowly add approximately 80% of the required TrichoWash™, using diametric dilution;
4. Transfer to a light-resistant polyethylene dispensing container and bring to volume;
5. Adjust pH to 4.0–5.0 with triethanolamine, if needed.

F3. Spironolactone 1% in TrichoWash™

1. Weigh spironolactone in a hood;
2. Dissolve spironolactone with ethoxy diglycol, using a magnetic stirrer;
3. In an Unguator jar, weigh approximately 50% of the required TrichoWash™. Add the spironolactone/ethoxy diglycol solution, and then the rest of the required TrichoWash™;
4. Spin on Unguator (FagronLab, Scheßlitz, Germany) slowly, on direct speed 2/2/2/.
5. Transfer to a light-resistant polyethylene dispensing container and bring to volume;
6. Adjust pH to 4.0–5.0 with triethanolamine, if needed.

Table 1. Active Pharmaceutical Ingredients Studied and their Formulations.

API	F1	F2	F3	F4	F5	F6	F7
Caffeine	-	-	-	-	-	20 mg	-
Clobetasol propionate	0.5 mg	-	-	-	-	-	-
DMSO	-	0.02 mL	-	-	-	0.01 mL	-
Ethoxy diglycol	-	-	0.1 mL	-	-	-	0.2 mL
Finasteride	-	-	-	-	-	-	2.5 mg
Ketoconazole	-	20 mg	-	-	-	-	-
Latanoprost 50 mg/mL in DMSO	-	-	-	0.02 mL	-	-	0.02 mL
Menthol crystal	-	-	-	-	-	10 mg	-
Minoxidil	-	-	-	-	-	-	50 mg
Purified water	-	-	-	-	0.25 mL	0.05 mL	-
Pyridoxine hydrochloride	-	-	-	-	5 mg	5 mg	-
Spironolactone	-	-	10 mg	-	-	-	-
Vitamin A acetate	-	-	-	-	10 mg	-	-
Vitamin E succinate	-	-	-	-	10 mg	-	-
TrichoCond™	-	-	-	-	q.s. 1 mL	-	-
TrichoCream™	-	-	-	q.s. 1 g	-	-	-
TrichoSol™	-	-	-	-	-	-	q.s. 1 mL
TrichoWash™	q.s. 1 mL	q.s. 1 mL	q.s. 1 mL	-	-	q.s. 1 mL	-

F4. Latanoprost 0.1% in TrichoCream™

1. Measure required amount of latanoprost;
2. Weigh 50% of required TrichoCream™;
3. Incorporate latanoprost into TrichoCream™;
4. Add the remaining amount of required TrichoCream™ to Unguator jar and spin at normal speed;
5. Transfer to a light-resistant polyethylene dispensing jar;
6. Adjust pH to 4.0–5.0 with triethanolamine, if needed.

F5. Pyridoxine HCl 0.5%, Vitamin A acetate 1%, and Vitamin E succinate 12.1 IU in TrichoCond™

1. Weigh pyridoxine HCl, vitamin A acetate, and Vitamin E succinate in a hood;
2. Place vitamin A in purified water and heat to 50 °C and mix until homogeneously suspended;
3. Measure approximately 50% of the required TrichoCond™ (which is an emulsion) and incorporate Vitamin A, Vitamin E, and pyridoxine HCl into a paste for the solubilization of the APIs, using a glass mortar and pestle;

4. Once mixed, transfer to a light-resistant polyethylene dispensing container and bring to volume with TrichoCond™;
5. Adjust pH to 4.0–5.0 with triethanolamine, if needed.

F6. Caffeine 2%, menthol 1%, and pyridoxine HCl 0.5% in TrichoWash™

1. Weigh caffeine, menthol, and pyridoxine HCl in a hood;
2. Triturate and dissolve menthol in DMSO, using a separate glass mortar and pestle;
3. Heat purified water to 150 °C and dissolve caffeine, mixing;
4. Dissolve pyridoxine HCl in heated caffeine/water mixture, then let it achieve room temperature;
5. Tare a speed mixer jar and add the pyridoxine HCl/caffeine/water mixture and the menthol/DMSO mixture;
6. Bring to volume with the heated TrichoWash™ and lightly stir with a glass stir rod;
7. Transfer to a light-resistant polyethylene dispensing container;
8. Adjust pH to 4.0–5.0 with triethanolamine, if needed.

F7. Latanoprost 0.1%, minoxidil 5%, and finasteride 0.25% in TrichoSol™

1. Weigh minoxidil and finasteride in a hood;
2. Triturate and dissolve finasteride in ethoxy diglycol, using a magnetic stirrer;
3. Measure required amount of latanoprost;
4. Measure approximately 80% of the required TrichoSol™. Add finasteride/ethoxy diglycol, then dissolve minoxidil, with mixing;
5. Add latanoprost to the previous solution and mix well;
6. Transfer to a light-resistant polyethylene dispensing container and bring to volume with TrichoSol™;
7. Adjust pH to 4.0–5.0 with triethanolamine, if needed.

2.2. Compatibility Study

The API samples were assayed by high performance liquid chromatography (HPLC) at pre-determined time points to verify the compatibility of the API in the vehicles. Aliquots for quantification (variable for each API) were withdrawn and diluted to obtain work solutions in the concentration described in Table 2. Sampling times were initial (T = 0), 3 months (T = 3), and 6 months (T = 6), depending on the formulation. All products were stored at controlled room temperature (20–25 °C) throughout the whole study.

All products were assayed three times, and the results were expressed as the mean from the independent measurements. The evaluation parameter was the percent recovery, using the HPLC method (results given as percentage ± standard deviation).

Table 2. Chromatographic Conditions Used in the Compatibility Study.

Formulation	Mobile Phase Composition	Work Concentration (μg/mL)/Injection Volume (μL)	Column	Flux (mL/min)	Ultraviolet Detection Wavelength (nm)
F1	190 mL acetonitrile + 40 methanol + 170 mL 0.05 M monobasic sodium phosphate	40.0/10	C18, 150 × 4.6 mm	1.0	240
F2	400 mL water + 650 mL acetonitrile + 0.5 mL triethylamine	200.0/10	C18, 100 × 4.6 mm	2.0	240
F3	220 mL water + 255 mL acetonitrile + 50 mL methanol + 1.35 mL phosphoric acid	5.0/5	C18, 150 × 4.6 mm	1.0	230

F4	180 mL water + 1.1g potassium phosphate monobasic + 220 mL acetonitrile	50.0/4	C18, 300 × 3.9 mm	2.0	200
F5	10 mL glacial acetic acid + 0.6 g sodium 1-hexanesulfonate + 700 mL of water	50.0 (pyridoxine)/40	C18, 250 × 4.6 mm	1.5	280
F6	25 mL acetonitrile + 20 mL tetrahydrofuran + 955 mL 0.82 g/L of anhydrous sodium acetate	200.0 (caffeine), 50.0 (pyridoxine)/5	C18, 150 × 4.6 mm	1.0	275
F7	280 mL water + 1.1 g potassium phosphate monobasic + 220 mL acetonitrile	5.0 (latanoprost), 250.0 (minoxidil),12.5 (finasteride)/4.0	C18, 300 × 3.9 mm	2.0	200

F1 = clobetasol 0.05% in TrichoWash™; F2 = ketoconazole 2% in TrichoWash™; F3 = spironolactone 1% in TrichoWash™; F4 = latanoprost 0.1% in TrichoCream™; F5 = pyridoxine HCl 0.5%, vitamin A acetate 1% and vitamin E succinate 12.1 IU in TrichoCond™; F6 = caffeine 2%, menthol 1% and pyridoxine HCl 0.5% in TrichoWash™; F7 = latanoprost 0.1%, minoxidil 5% and finasteride 0.25% in TrichoSol™.

2.3. Chromatographic Conditions

All analyses were performed by stability-indicating HPLC methods using the conditions described in Table 2. The APIs contents were calculated by direct comparison of their area with the one of the standard. All samples were diluted to the work concentration with mobile phase, and then filtered through a 0.45 mm filter membrane and degassed using an ultrasonic apparatus for 30 min immediately before use. The standards were also diluted in the mobile phase. All columns were from Phenomenex (Torrance, CA, USA) and were connected with a pre-column with the same packing (4.0 × 3.0 mm, 5 mm) from the same manufacturer. All volumetric glassware and analytical balances used were calibrated.

3. Results

At each sampling time, the visual appearance of the products was also evaluated to verify their homogeneity and physical compatibility (data not shown). Throughout the whole study, none of the following phenomena were observed: caking, flocculation, macroscopically visible crystal growth, odor generation, phase separation, precipitation, or turbidity.

The chemical compatibility results are shown in Table 3 and Figure 1, expressed as the percent of recovery in relation to T = 0. For the products to be considered stable, the relative percentage recovery should lie within 90% to 110%.

In our study, a beyond-use date (BUD) of 6 months was observed for all products stored at room temperature, except for the ones containing latanoprost, which presented a BUD of 3 months.

In the absence of compatibility information for a specific formulation, USP <795> (Pharmaceutical compounding—nonsterile preparations) can be used as a guideline, which advises a beyond-use date of no more than 30 days [15]. The longer BUD of 3 or 6 months presented in this study offers increased convenience for both the compounding pharmacist and the patient.

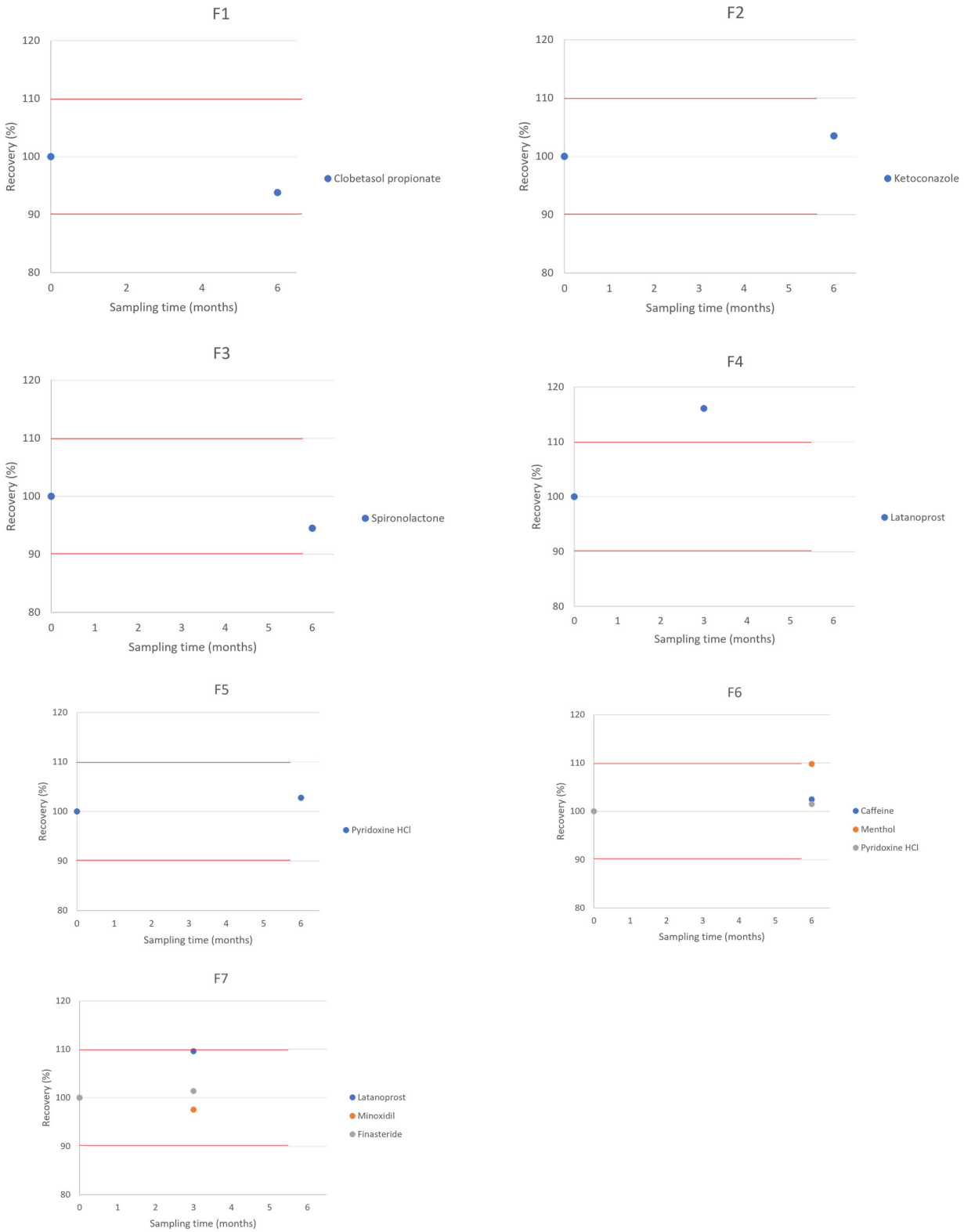

Figure 1. Compatibility of the Selected APIs in the Hair Vehicles. Red lines represent the lower and upper limits, corresponding to 90% and 110% of labeled concentration.

Table 3. Compatibility of the Active Pharmaceutical Ingredients in the Hair Vehicles.

Elapsed Time (Months)	% Recovery (Room Temperature, 20–25 °C)
Clobetasol propionate 0.05%—compounded in TrichoWash™	
T = 0	100.0
T = 6	93.8
Ketoconazole 2%—compounded in TrichoWash™	
T = 0	100.0
T = 6	103.5
Spironolactone 1%—compounded in TrichoWash™	
T = 0	100.0
T = 6	94.5
Latanoprost 0.1%—compounded in TrichoCream™	
T = 0	100.0
T = 3	106.6
Pyridoxine HCl 0.5%—compounded with vitamin A acetate 1% + vitamin E succinate 12.1 IU in TrichoCond™	
T = 0	100.0
T = 6	102.78
Caffeine 2%—compounded in combination with menthol 1% + pyridoxine HCl 0.5%, in TrichoWash™	
T = 0	100.0
T = 6	102.5
Menthol 1%—compounded in combination with caffeine 2% + pyridoxine HCl 0.5%, in TrichoWash™	
T = 0	100.0
T = 6	109.8
Pyridoxine HCl 0.5%—compounded in combination with caffeine 2% + menthol 1%, in TrichoWash™	
T = 0	100.0
T = 6	102.5
Latanoprost 0.1%—compounded in combination with minoxidil 5% + finasteride 0.25%, in TrichoSol™	
T = 0	100.0
T = 3	109.6
Minoxidil 5%—compounded in combination with latanoprost 0.1% + finasteride 0.25%, in TrichoSol™	
T = 0	100.0
T = 3	97.56
Finasteride 0.25%—compounded in combination with latanoprost 0.1% + minoxidil 5%, in TrichoSol™	
T = 0	100.0
T = 3	101.4

Lower and upper limits were set as 90% and 110% of labeled concentration, respectively. System suitability was checked for all analyses, with a relative standard deviation lower than 2%.

4. Conclusions

We have tested seven formulations using TrichoTech™ hair vehicles, and found the following beyond-use dates (BUD):

- F1 = clobetasol 0.05% in TrichoWash™. BUD = 6 months.
- F2 = ketoconazole 2% in TrichoWash™. BUD = 6 months.
- F3 = spironolactone 1% in TrichoWash™. BUD = 6 months.
- F4 = latanoprost 0.1% in TrichoCream™. BUD = 3 months.
- F5 = pyridoxine HCl 0.5%, vitamin A acetate 1% and vitamin E succinate 12.1 IU in TrichoCond™. BUD = 6 months.
- F6 = caffeine 2%, menthol 1%, and pyridoxine HCl 0.5% in TrichoWash™. BUD = 6 months.

- F7 = latanoprost 0.1%, minoxidil 5%, and finasteride 0.25% in TrichoSol™. BUD = 3 months.

All formulations presented a beyond-use date of at least 3 or 6 months. Thus, this study showed that the APIs were all compatible with the TrichoTech™ vehicles in the conditions described, reinforcing that the vehicles are compatible with a wide range of APIs. These results validate that the TrichoTech™ hair vehicles are an adequate choice for use by compounders.

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